REMARKS/ARGUMENTS

Status of Claims

Claims 1, 4, 6, 7, 8, 18, 26, 28, 29, 30, 35, 36, 37, 38, 44, and 45 have been amended.

Claims 3, 5, 23-24, 31-34, 39-43, and 46-52 have been canceled.

New claims 53-56 have been added.

Thus, claims 1, 2, 4, 6-22, 25-30, 35-38, 44-45, and 53-56 are currently pending in this application.

Applicants hereby request further examination and reconsideration of the presently claimed application.

Restriction Requirement

Applicants affirm the election of group I, claims 1-22, 25-42 and 44-45. Furthermore, Applicants have amended the pending claims to recite the elected species, namely a pharmaceutical formulation comprising azelastine and fluticasone.

New Claims

Applicants have added new claims 53-54 directed to specific combinations of azelastine and specific pharmaceutically acceptable esters of fluticasone, which are supported by paragraph 0045 of the published application. Further, Applicants have added new claims 55-56, which mirror existing claims 28 and 29, and are drawn to a nasal spray as disclosed by paragraph 0010 of the published application. The new claims are patentable for the reasons set forth below.

Claim Rejections – 35 U.S.C. § 112

Claims 6 and 18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claim 6 to remove the term "about." Applicants have also

amended claim 18 to remove the recitation of a narrower range of values. In consideration of the foregoing, Applicants respectfully request withdrawal of the rejections.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 2, 4, 7, 9-10, 12-21, 30-31, and 44-45 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Cramer, European Patent No. 0780127 (hereinafter "*Cramer*"). Applicants note that claim 5 was not rejected as being anticipated by *Cramer*. Applicants have amended claim 1 to incorporate the limitations of now canceled claim 5 and respectfully submit that claims 1, 2, 4, 7, 9-10, 12-21, 30-31, and 44-45 are not anticipated by *Cramer*.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 2, and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Malmqvist-Granlund, et al., U.S. Patent No. 6,391,340 (hereinafter "*Malmqvist-Granlund*"). Applicants note that claim 5 was not rejected as being obvious in view of *Malmqvist-Granlund.* Applicants have amended claim 1 to incorporate the limitations of now canceled claim 5 and respectfully submit that claims 1, 2 and 6 are not obvious over *Malmqvist-Granlund.*

Claims 5 and 35-38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer*. Claims 22 and 26-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Modi, U.S. Patent No. 6,294,153 (hereinafter "*Modi*"). Claims 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Alfonso, et al., U.S. Patent No. 6,017,963 (hereinafter "*Alfonso*"). Accordingly, the pending claims stand or fall on the above-recited application of the primary reference, *Cramer*, alone or in combination with the secondary references, *Modi* or *Alfonso*, to independent claims 1, 26, 28, and 29. Applicants respectfully submit the pending claims are patentable because the broad genus disclosed in the primary reference does not render obvious the Applicants' claimed species directed to a

pharmaceutical formulation comprising azelastine and fluticasone. Further, Applicants submit herewith objective evidence of nonobviousness in that the claimed species directed to a pharmaceutical formulation comprising azelastine and fluticasone displays unexpectedly beneficial properties, is commercially successful, and fills a long felt but unsolved need.

The Legal Standard for Obviousness

The MPEP provides that "establishing a *prima facie* case of obviousness" requires, "the clear articulation of the reason(s) why the claimed invention would have been obvious." *See* MPEP § 2142. The MPEP also acknowledges that "[t]he Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." *See* MPEP § 2143.

Moreover, in *KSR Int'l Co. v. Teleflex, Inc.*, the United States Supreme Court explained that, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art," but, additionally whether "the claim extends to what is obvious." *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1397 (2007). Expounding on its edict, the Supreme Court went on to opine that an obviousness determination is based upon a "proper application of *Graham*," including consideration of "secondary factors" that may weigh against an obviousness determination. *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1399 (citing *Graham v. John Deere Co. of Kansas City, et al.*, 383 U.S. 1, 148 USPQ 459 (1966)). The Office Action states:

> [t]he factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
>
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining the differences between the prior art and the claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

See Office Action at 10. In an attempt to satisfy the factual inquiries set forth in *Graham*, the Office Action addresses the "determining the scope and contents of the prior art" and "ascertaining the differences between the prior art and the claims at issue" portions of the *Graham* factual inquiries. However, the Office Action is silent with regards to the "resolving the level of ordinary skill in the pertinent art" and "considering objective evidence present in the application indicating obviousness or nonobviousness" portions of the *Graham* factual inquiries.

A. *Cramer* does not fairly suggest the elected species

In ascertaining the difference in the prior art and claim 5, the Office Action acknowledges "Cramer does not exemplify a composition comprising azelastine and fluticasone." *See* Office Action at 12. As such, the Office Action retreats to a "rationale-based" obviousness rejection based on the conclusion that:

> one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a gluccocortoid (i.e. fluticasone) and antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis.

See Office Action at 12.

The Office Action then supports its "rationale-based" rejection by stating, "the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made **because the prior art is fairly suggestive of the claimed invention**." *See* Office Action at 13 (emphasis added). As noted previously, "establishing a *prima facie* case of obviousness" requires, "the clear articulation of the reason(s) why the claimed invention would have been obvious." *See* MPEP § 2142. The Office Action's conclusion does not support a *prima*

facie case of obviousness because the Office Action does not clearly articulate why the claimed invention would be obvious.

The Office Action's reliance and discussion of *Cramer* does not articulate why the claimed pharmaceutical formulation comprising azelastine and fluticasone would be obvious in view of *Cramer's* general disclosure that mixtures of glucocorticoids and mixtures of antihstamines could be combined. The total number of **possible glucocorticoids specified in *Cramer* is six** (*beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone and budesonide*) and the **total number of antihistamines is three** (*cetirizine, loratadine, azelastine*). Accoringly, there is a total of eighteen different combinations disclosed in *Cramer*. The present application claims just one of these combinations, and it is common ground that this particular combination (fluticasone and azelastine) is not explicitly mentioned in *Cramer*. The number of possible combinations rises exponentially when considering the breadth of the disclosed combinations of racemates, salts, and mixtures of the glucocorticoid and antihistamine agents.

As such, *Cramer*'s disclosure cannot be "fairly suggestive of the claimed invention," *see* Office Action at 13, because, as the MPEP states, the rationale for supporting an obviousness determination requires, "choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success." *See* MPEP § 2143; *see also KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1397 (a combination of elements is obvious if "there are finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue."). Clearly, *Cramer*'s recitation of the possibility of innumerous combinations of compounds does not disclose a "finite number of identified, predictable solutions." *See id.*

Based on the foregoing, Applicants respectfully submit that the Office Action does not present a *prima facie* case of obviousness with regard to the instant claims.

B. Secondary considerations indicate that the combination of azelastine and fluticasone is nonobviousness

Assuming, without conceding, that the Office Action's "rationale and motivation" discussion is sufficient, nevertheless, the Office Action's suggestion of a *prima facie* case of obviousness must fail because the unaddressed "secondary considerations" described below render the instant claims nonobvious. *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1399. Applicants provide herewith a Rule 1.132 declaration of inventor Geena Malhotra and the accompanying Exhibits A-C setting forth evidence of the following secondary considerations of nonobviousness.

1. The combination of azelastine and fluticasone displays unexpected, beneficial results

A showing of unexpected results may rebut a *prima facie* case of obviousness, and is particularly applicable in the inherently unpredictable chemical arts where minor changes may yield substantially different results. *See e.g.*, *In re Soni*, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). Exhibit A of the declaration demonstrates that the claimed pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial stability. As noted in paragraph 2 of the declaration:

> The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

These tests demonstrate that there is a clear unexpected advantage in product stability in formulating azelastine with fluticasone rather than with other steroids such as budesonide.

Improved product stability is extremely important in pharmaceutical compositions as is understood by those skilled in the art.

Furthermore, Exhibits B1 and B3 of the declaration demonstrate that a pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial efficacy when administered to patients. Specifically, Exhibit B1 notes that the use of DUONASE (a commercial pharmaceutical formulation comprising azelastine and fluticasone) "is very effective when compared [to] the available other nasal sprays." Likewise, Exhibit B3 notes (with emphasis added):

> DUONASE Nasal Spray is very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "DUONASE Nasal Spray".

Likewise, the remainder of the doctor statements in Exhibit B extol the therapeutic benefits of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Such recognition by skilled artisans of the merits of the invention is further evidence of nonobviousness. *See Akzo N.V. v. United States Int'l Trade Comm'n*, 1 USPQ2d 1241, 1247 (Fed. Cir. 1986). These doctor statements demonstrate a clear, unexpected advantage in treatment efficacy, namely that the combination of azelastine and fluticasone provides a synergistic benefit in efficacy over azelastine alone or fluticasone alone.

As set forth above, the declaration provides strong evidence that the claimed pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial stability, and that upon administration to a patient, unexpected and beneficial enhanced efficacy is observed. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of these unexpected results.

2. The combination of azelastine and fluticasone is commercially successful

Commercial success is a strong factor favoring nonobviousness. *See e.g., Akzo N.V.* at 1246. As noted in paragraph 3 of the declaration, a pharmaceutical formulation comprising azelastine and fluticasonse is commercially available where approved as DUONASE nasal spray. The doctor statements set forth in Exhibit B provide further evidence of the commercial success of DUONASE nasal spray. Furthermore, as noted in paragraph 5 of the declaration the present application claiming a pharmaceutical formulation comprising azelastine and fluticasonse is licensed to Meda Pharmaceuticals, which specializes in respiratory, allergy, and cough-cold products. Given its expertise and knowledge in the field of treatment, the willingness of Meda Pharmaceuticals to license the pending application is further evidence of the commercial success of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of its commercial success.

3. The combination of azelastine and fluticasone fills a long-felt need

As set forth in *Graham*, the existence of a long-felt and unsolved need in the art is further evidence of nonobviousness. Applicants note that *Cramer* was published on June 25, 1997, which was over 10 years ago. Nonetheless, as noted in paragraph 5 of the declaration, inventor Geena Malhotra is unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid. Likewise, the doctor statement of Exhibit B4 notes that:

> I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.
>
> The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

Such "[f]irsthand practical knowledge of unsolved needs in the art, by an expert, is evidence of the state of the art." *See In re Piasecki*, 223 USPQ 785, 789 (Fed. Cir. 1984). Applicants respectfully submit that the evidence establishes a long-felt need dating back to 1993 that continued unsolved even after the subsequent publication of *Cramer* in 1997. Applicants further submit that the lack of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid further evidences a long-felt need and the failure of others to address the need prior to the present invention. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious given that it meets the long-felt need outlined above.

4. The secondary considerations require a finding of nonobviousness

As set forth above, the claimed pharmaceutical formulation comprising azelastine and fluticasone displays unexpected, beneficial results; is commercially successful; and fills a long-felt need in the art. Accordingly, the totality of the secondary considerations requires a finding that the pending claims are not obvious, and therefore patentable, in view of the prior art of record.

CONCLUSION

Consideration of the foregoing amendments and remarks, reconsideration of the application, and withdrawal of the rejections are respectfully requested by Applicants. No new matter is introduced by way of the amendment. It is believed that each ground of rejection raised in the Office Action dated January 23, 2009 has been fully addressed. If any fee is due as a result of the filing of this paper, please appropriately charge such fee to Deposit Account Number 50-1515 of Conley Rose, P.C., Texas. If a petition for extension of time is necessary in order for this paper to be deemed timely filed, please consider this a petition therefore.

If a telephone conference would facilitate the resolution of any issue or expedite the prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,
CONLEY ROSE, P.C.

Date: 7-23-09

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